Effect of Lithium on Aggression, Mania- and Permselective Membranes

The effect of lithium ions on behaviour has been established beyond doubt during the last decade. Lithium ions reduce aggressive behaviour in fish and rodents[1,2] and have been effective in the treatment of human mania[3–6] and beside this sometimes even of human depression[7–10]. Some biochemical reactions influenced by lithium have been discussed in a review[11], such as inhibition of carbohydrate transport[12,13] and influence on cyclic AMP metabolism[14] and on the combined effect with dopamine and vanillyl mandelic acid[15]. However, the impression remained that a basic link is still missing in the explanation of the physiological effect of lithium ions[11].

Behaviour is controlled by the nervous system. The excitation wave along the neurons and synaptic transmission takes place along and across the membranes of neuron and synapsis. It may therefore be pertinent that the lithium ion also has a strong effect on certain ion-permselective membranes which in some respects resemble neural membranes and may sometimes serve as their simplified model.

Permselective membranes selectively allow the passage of anions or cations according to whether the fixed ionic groups within them are positively or negatively charged. Such membranes made of polyethylene-phosphonic acid increase their resistance from a few ohms per cm^2 to some 100,000 ohms when they are transferred from an alkaline into an acid solution. However, their resistance is also increased a 1000 fold in the presence of lithium ions, even in $1N$ LiOH which is strongly alkaline[16,17]. Their phosphonic acid content determines how strongly and in which pH range resistance changes most quickly with pH. The strongest pH dependence is often in the physiological range of about pH 7.

The explanation of these phenomena is as follows: Phosphonic acids gradually deionize in acid media. Consequently they also lose swelling water, and this is the reason that the number of aqueous channels across the membrane and hence the conductivity decreases. We found that these membranes are more open to Na^+ than to K^+ in acid and neutral pH ranges[16]. This means that the size of the unhydrated ion determines permeability in this domain. To confirm this conclusion we also used Li^+, as the smallest alkali ion. Surprisingly, it was found to 'close' the membrane similarly to H^+, but even in strongly alkaline solutions. This must mean that the small Li^+ ion is attracted so strongly by the phosphanate ion that it loses its hull of hydrate water molecules and becomes attached to the phosphonate ions. The latter are thus deionised, and also lose their hydration water, so that the membrane shrinks and its conductivity decreases strongly. It should be remembered that inorganic Li_3PO_4 is also slightly soluble in water.

The physiological membranes which surround neurons and are responsible for their excitability always contain phosphate groups bound in their phospholipids. It seems more than probable that some of these phosphate groups react with Li^+ similarly to the phosphonate groups of our artificial membranes. Although spiking of nerves is only slightly impeded when Li^+ is substituted for Na^+ in the external solution around an axon[18], the recovery period after spiking is 10–25 times longer in Li^+ than in Na^+ solutions and it blocks impulse transmission in ganglia[19,20]. The simple ionic combination of Li^+ with phosphate sites in the phospholipid membrane is probably dependent on the species of phospholipid. One would assume that acidic lipids like phosphatidic acid, phosphatidyl-inositol or phosphatidyl-serine combine more strongly with Li^+ than the amphoteric species lecithin and phosphatidyl-ethanolamine in which the phosphate can be bound to ammonium or amino groups. This could allow different parts and actions of the neuron to be influenced by Li^+ to a different extent. But it seems very probable that Li^+ increases the electric resistance of some nerve membranes in the same way as it increases the resistance of our artificial membrane, and that nerve membranes which become sluggish in their electrophysiological behaviour ultimately also reduce more violent psychological effects.

Zusammenfassung. Nachweis, dass Li^+-Ionen den elektrischen Widerstand von permselektiven Membranen, welche Phosphatgruppen enthalten, stark erhöhen. Die beruhigende Wirkung der Li^+-Ionen bei psychischen Störungen könnte damit zusammenhängen.

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1 M. L. WEISCHER, Psychopharmacologia *15*, 245 (1969).
2 M. H. SHEARD, Nature, Lond. *228*, 284 (1970).
3 J. F. J. CADE, Med. J. Austr. *2*, 349 (1949).
4 S. GERSHON and A. YUWILER, Neuropsychiatria *1*, 229 (1960).
5 M. SCHOU, in *Antidepressant Drugs* (Eds. S. GARATTINI and M. N. G. DUKES; Excerpta Medica Foundation, Amsterdam 1967), p. 80.
6 M. H. SHEARD, Nature, Lond. *230*, 113 (1971).
7 P. BAASTROUP and M. SCHOU, Arch. gen. Psychiat. *16*, 162 (1967).
8 R. R. FREVE and S. R. PLATINAU, Am. J. Psychiat. *125*, 487 (1968).
9 F. K. GOODWIN, D. L. MURPHY and W. E. BUNNEY JR., Arch. gen. Psychiat. *21*, 486 (1969).
10 A. A. GATOZZI, U. S. Govt. Printing Office, National Clearing House of Mental Health, Information No. 5033 (1970).
11 I. B. PEARSON and F. A. JENNER, Nature, Lond. *232*, 532 (1971).
12 C. BATTACHARYA, Biochim. biophys. Acta *135*, 466 (1971).
13 J. BOSACKOVA and B. K. CRANE, Biochim. biophys. Acta *102*, 423 (1965).
14 T. DOUSA and O. HECHTER, Life Sci. *9*, 765 (1970).
15 F. S. MESSIHA, D. AGALLIANOS and C. CLOWER, Nature, Lond. *225*, 868 (1970).
16 D. KERTÉSZ and F. DE KÖRÖSY, Israel J. Chem. *6*, 103 (1968).
17 D. KERTÉSZ, F. DE KÖRÖSY and E. ZEIGERSON, Desalination *2*, 161 (1967).
18 E. OVERTON, Pflügers Arch. ges. Physiol. *92*, 346 (1902).
19 R. D. KEYNES and R. C. SWAN, J. Physiol., Lond. *147*, 591 (1959).
20 R. D. KEYNES and R. C. SWAN, J. Physiol. *147*, 626 (1959).

LSD Effects on Signal-to-Noise Ratio and Lateralization of Visual Cortex and Lateral Geniculate During Photic Stimulation

Signal-to-noise ratios and modulation period changes of visual cortex and lateral geniculate body have been described by TREHUB[1,2], during contralateral and ipsilateral photic stimulation. More recently this author[3] postulated, on the same experimental grounds, that the brain functions as a coherent signal detector.